Remarks

The Examiner stated on page 2 of the July 7, 2003 Office Action that groups I and III will be taken together for the present examination. According to the October 8, 2002 Restriction Requirement, group I is claims 1-5, while group III is claims 31-37 and 40. Group IV is claims 38 and 39. However, the July 7, 2003 Office Action appears to address claims 1-5, 38, and 39. corresponding to groups I and IV. As a result, Applicants present claims 1-5, and 31-40 for examination – with clarification later of any claims that were unexamined – although Applicants respectfully submit that examination of claims 1-5 and 31-40 can be examined together without undue burden to searching.

Thus, the claims are 1-5, and 31-40. Claims 6-30 have been cancelled as being directed to unelected subject matter without prejudice to Applicants filing any applications to such subject matter.

Information Disclosure Statement

The Examiner noted that the references submitted in the Information Disclosure Statement (IDS) on September 4, 2002 were not received by the Examiner. Applicants respectfully enclosed a copy of that IDS, together with copies of the foreign patent publications and scientific publications in Applicants' previous response. Copies of the U.S. Patents were not enclosed as they should not be sent according to present PTO practice. Further, Applicants respectfully requested that foreign language patent publication No. EP 0 722 943 be replaced with its equivalent U.S. Patent No. 5,866,571 issued February 2, 1999; EP 0 722 944 with its equivalent U.S. Patent No. 5,861,404 issued January 19, 1999; EP 1 074 258 with its equivalent U.S. Patent Publication No. 200201199 published August 29, 2002; WO 00/12501 with its equivalent U.S. Patent No. 6,436,952 issued August 20, 2002; WO 00/26201 with its equivalent U.S. Patent No. 6,376,493 issued April 23, 2002; WO 99/65880 with its equivalent U.S. Patent No. 6,417,188 issued July 9, 2002; WO 98/17668 with its equivalent U.S. Patent No. 6,130,223 issued October 10, 2000; WO 98/14448 with its equivalent U.S. Patent No. 6,265,577 issued July 24, 2001; WO 98/06722 with its equivalent U.S. Patent No. 6,110,920 issued August 29, 2000; WO 97/24334 with its equivalent U.S. Patent No.

6,166,219 issued December 26,2000. Accordingly, the above foreign language publications have been omitted and their U.S. equivalent patents have been noted on the submitted copy of the previously submitted form 1449. Further, Applicants respectfully enclosed a copy of the return postcard from the previously submitted IDS, which indicated that the PTO received the IDS with its cited references and the required Form 1449. Applicants respectfully request entry of the IDS and the Examiner's acknowledgement of the references by initialing the Form 1449 appropriately.

Rejections under 35 USC 112:

The term "substantial" has been rejected as indefinite. Applicants respectfully submit that one in the art readily understands the term.. Nevertheless, the term is defined in the specification at, for example, page 9, third full paragraph. Accordingly, Applicants respectfully submit that the rejection has been overcome and requests its withdrawal.

Rejections under 35 USC 103:

Claims 1-5, 38, and 39 have been rejected as being unpatentably obvious over U.S. Patent No. 6,080,548 ("Au-Young"), in light of U.S. Patent No. 6,569,638 ("Weinstein"), 1992:210056 CAPLUS ("Lugnier"), and 1979:97384 CAPLUS ("Greenwald"). Claim 5 adds U.S. Patent No. 6,555,547 ("Pamukcu") for recitation of IC_{50} values.

Applicants respectfully submit that the Examiner has not made a *prima facie* case for obviousness because a crucial element – the connection of PDE2 to scleroderma – is not disclosed by the cited references in any combination or alone. While Au-Young discloses that an antagonist of PDE8 may treat scleroderma (col. 21, lines 44-57), the reference makes clear that PDE8 is different from the other PDEs (col. 1, lines 34-61). Indeed, the only stated homology to other PDEs is to PDE4 (col. 21, lines 17-18) – and only to 22-29% homology (col. 12, lines 55-64). Thus, from Au-Young, treatment of scleroderma can be imputed to, at most, possibly PDE4 inhibitors as well as PDE8 inhibitors.

Au-Young does state that "PDE8A(E) was inhibited by dipyridamole [which is an] inhibitor of PDE5" (col. 12, lines 36-37). Lugnier, and Greenwald discloses that

dipyridamole is an of PDE2 and PDE4 without inhibiting COX. There is no disclosure or suggestion of dipyridamole being used to treat scleroderma. Thus, there is no disclosure of a PDE2 inhibitor being used to treat scleroderma. Even if one were to make the conceptual leap of utilizing dipyridamole to treat the wide variety of disorders that include "AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, deramtomyositis, diabetes mellitus, emphysema, erythema nodosum, atrophic gastritis, glomerulonephritis, gout, Grave's disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections; and trauma," as disclosed for antagonists of PDE8 in Au-Young (col. 21, lines 46-60) – how would one isolate scleroderma from the list? And there is no disclosure that it is inhibition of PDE2 that is useful for treatment of scleroderma, as claimed in the present invention.

By contrast, the present invention discloses at, for example, page 49, last full paragraph, that "the inhibition of only PDE4 or PDE5 alone (i.e. without the inhibition of PDE2) is not sufficient to induce apoptosis in U937 cells." Accordingly, Applicants respectfully submit that the Examiner has impermissibly used hindsight, impermissibly with the present invention as a template, to pick out scleroderma from the long list of Au-Young, and to pick out PDE2 from the possible inhibition properties of dipyridamole, in order to form a speculative connection of PDE2 to scleroderma. Pamakcu does not provide a connection of PDE2 to scleroderma.

Accordingly, Applicants respectfully submit that the rejection has been overcome and request their withdrawal.

Conclusion:

Applicants respectfully submit that the claims are in condition for allowance and respectfully request a Notice to that effect. Attorney for Applicants can be reached at the telephone number and address below. Commissioner is authorized to charge any

deficiencies and credit any overpayment to OSI Pharmaceuticals, Inc. Deposit Account No. **502783**.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date appearing below.

OSI PHARMACEUTICALS, Inc.
By Shu M. Lee **Date** April 7, 2004

Very truly yours,

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